Complete Summary

GUIDELINE TITLE

Adjuvant systemic chemotherapy, following surgery and external beam radiotherapy, for adults with newly diagnosed malignant glioma.

BIBLIOGRAPHIC SOURCE(S)

Neuro-Oncology Disease Site Group. Perry J, Zuraw L. Adjuvant systemic chemotherapy, following surgery and external beam radiotherapy, for adults with newly diagnosed malignant glioma [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2004 Jun [online update]. 14 p. (Practice guideline report; no. 9-2). [32 references]

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SCOPE

DISEASE/CONDITION(S)

Newly diagnosed malignant glioma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Neurology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate if chemotherapy should be recommended, following surgery and external beam radiotherapy, to adults with newly diagnosed malignant glioma in order to improve overall survival and/or quality of life

TARGET POPULATION

Adults with newly diagnosed malignant glioma who have undergone surgery and external beam radiotherapy

INTERVENTIONS AND PRACTICES CONSIDERED

1. Radiotherapy alone
2. Radiotherapy plus chemotherapy, including bleomycin, cisplatin, 5-fluorouracil, nitrosourea, lomustine (CCNU), carmustine (BCNU), dibromodulcitol (DBD), methyl-CCNU, dianhydrogalactitol (DHG), dacarbazine (DTIC), procarbazine, vincristine, epipodophyllotoxin (VM-26)

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Adverse effects
- Health status
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (1966 to June 2004), CANCERLIT (1983 to October 2002), and the Cochrane Library (2004, Issue 2) databases were searched with no language restrictions. "Glioma" (Medical subject heading [MeSH]) was combined with "chemotherapy, adjuvant" (MeSH). These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, meta-analyses, and randomized controlled trials. In addition, the Physician Data Query (PDQ) clinical trials database (www.cancer.gov/search/clinical_trials/, searched May 21, 2003) and the proceedings of the 1997 to 2004 meetings of the American Society of Clinical Oncology (ASCO) were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by one reviewer, and the reference lists from these sources were searched for additional trials.

Inclusion Criteria

1. All randomized controlled trials (RCTs) of adjuvant chemotherapy for malignant glioma were included. Trials could be of single- or multi-agent regimens, but these regimens had to be compared with a no-chemotherapy control arm. The Neuro-oncology Disease Site Group members elected to include early studies that used what are now considered to be unacceptable methods of allocation (i.e., by birth-year or sequential assignment) because data from these studies are frequently cited and were used in a subsequent published meta-analysis. In some instances, a randomized trial was reported in more than one publication or as a single-institution experience within a larger multicentre trial; these studies were included in order to judge their quality and any bias that their inclusion in subsequent overviews may have introduced.
2. As the primary outcomes of interest were overall survival, median survival or survival rates had to be reported. Quality of life (QOL) was also considered.
3. Full reports and abstracts were considered.

Exclusion Criteria

1. Phase I and II studies were not included because of the availability of randomized trials. Letters, editorials, and review articles were not considered.
2. Trials were excluded if they compared active regimens rather than having a no-chemotherapy control arm.
3. Studies of non-systemic treatments, such as the intracavitary placement of carmustine wafers, were also excluded.

NUMBER OF SOURCE DOCUMENTS

Two published meta-analyses and 24 randomized controlled trials were identified and reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The authors considered performing their own meta-analysis of all relevant randomized controlled trials (RCTs). However, they felt that the heterogeneity within these studies precluded a valid meta-analysis, if performed in the

traditional fashion. Meta-analysis is open to misinterpretation when results are combined, even against better judgment, simply to create a large sample size. Heterogeneity of a meta-analysis results from variations in inclusion criteria, outcome measures, and interventions. However, the Medical Research Council (MRC-UK) had performed a meta-analysis by obtaining original individual patient data from the randomized trials.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Members of the Neuro-oncology Disease Site Group (DSG) agreed that, based upon the current evidence, it was reasonable not to recommend the routine use of adjuvant chemotherapy for patients with malignant glioma. Extensive consideration was given to the pre-treatment factors that might predict a higher chance of treatment response; nevertheless, even in patients with a predictably high probability of response to chemotherapy, there are no data from randomized controlled trials (RCTs) to confirm a survival advantage from adjuvant chemotherapy. In addition, the dilemma of expected survival gain versus treatment toxicity and impact upon quality of life remains unexplored. Ongoing randomized controlled trials will help to clarify the optimal timing of procarbazine, lomustine, vincristine (PCV) chemotherapy for the most chemosensitive group of patients, those with anaplastic oligodendroglioma. Newer schedules and new chemotherapy agents, such as temozolomide, are also promising. Some astrocytic malignant gliomas are chemosensitive (a minority) but which ones, or why, is not yet clear. At present, allowing individualized consideration of adjuvant chemotherapy for patients with anaplastic oligodendroglioma, anaplastic astrocytoma and young patients with any type of malignant glioma is a reasonable option. Implicit in the designation of chemotherapy as an "option" for these patient groups is the recommendation that patients be provided with information about the controversies surrounding the benefit and optimal timing of such chemotherapy. Participation in ongoing clinical trials should be encouraged.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 67 practitioners in Ontario (13 medical oncologists, 15 radiation oncologists, 22 surgeons, 15 neurologists, one hematologist, and one pathologist). The survey consisted of 21 questions about the quality of the practice-guideline-in-progress report and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Neuro-oncology Disease Site Group (DSG) has reviewed the results of the survey.

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. All 11 members of the PGCC returned ballots. Ten PGCC members approved the practice guideline report as written, with two members providing suggestions for consideration by the DSG. One member conditionally approved the guideline, provided that the Neuro-oncology DSG include a firmer statement regarding the reliability of the recent BR-05 randomized controlled trial as the most compelling source of evidence. The Neuro-oncology DSG revised the Interpretative Summary to reflect the importance of BR-05 as the most compelling source of evidence.

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Neuro-oncology DSG.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- The routine use of current adjuvant chemotherapy regimens for patients with malignant glioma is not recommended.
- Younger patients, patients with anaplastic (grade 3) astrocytoma, and patients with pure or mixed oligodendroglioma, are more likely to harbour chemosensitive tumours, and adjuvant chemotherapy may be an option in these cases. However, there is no evidence of a survival advantage from adjuvant chemotherapy even in these situations, and treatment-related adverse effects and their impact upon quality of life are poorly studied.
- Patients should be provided with information about the controversies surrounding the benefit and optimal timing of such treatment.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by meta-analyses and randomized controlled trials (RCTs).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Twenty-four heterogeneous randomized controlled trials and two meta-analyses incorporating some of these trials variably detected either no advantage or a small survival advantage in favour of adjuvant chemotherapy. These studies often did not consider quality of life as an outcome variable. The most contemporary and largest trial reported a slight survival advantage in favour of adjuvant chemotherapy compared with no-chemotherapy controls in patients with anaplastic astrocytoma or glioblastoma.

POTENTIAL HARMS

Scales for toxicity assessment were commonly used in the early trials (prior to 1994). However, brain tumour patients may have disease-specific acute and delayed adverse effects not captured in all-purpose toxicity scales such as the National Cancer Institute Common Toxicity Criteria. For example, the impairment of neurocognitive function likely represents an important outcome to patients and may reflect the impact of disease or the impact of treatment. In general, the acute adverse effects of chemotherapy were well tolerated by most patients; unfortunately, many of the early randomized controlled trials excluded from the analysis patients with the most severe toxicity. Most chemotherapy regimens used in these studies were associated with acceptable myelotoxicity. Nausea and vomiting were often problematic.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline considers chemotherapy in the adjuvant setting only and should not discourage the consideration of chemotherapy for selected patients at the time of tumour progression or in the context of clinical trials evaluating new treatment regimens at any point in the disease.
- The results of the Medical Research Council meta-analysis need to be interpreted with caution. There were differences in the designs of the randomized controlled trials included in the meta-analysis, including various radiotherapy regimens. Also, of the 12 studies included in the meta-analysis, eight were published 20 or more years ago.
- Virtually all of the early randomized controlled trials suffered from methodological or analytical flaws that preclude consideration as high-quality evidence for use in the guideline development process. The four pre-treatment prognostic variables of age, performance status, degree of surgical resection, and tumour grade are key determinants of patient outcome. Various combinations of these prognostic factors had more influence upon patient survival than did treatment itself in many analyses.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any

kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Mar 10 (revised online 2004 Jun)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Neuro-oncology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Neuro-oncology Disease Site Group (DSG) disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Adjuvant systemic chemotherapy, following surgery and external beam radiotherapy, for adults with newly diagnosed malignant glioma. Summary. Toronto (ON): Cancer Care Ontario (CCO). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 30, 2004. The information was verified by the guideline developer on July 19, 2004.

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